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William E. Collins
CNI Aviation, LLC
Ada, OK 74820

Michael E. Wayda
Civil Aerospace Medical Institute
Federal Aviation Administration
Oklahoma City, OK 73125

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16. Abstract

An index to Federal Aviation Administration Office of Aerospace Medicine Reports (1964-2006) and Civil Aeromedical Institute Reports (1961-1963) is presented for those engaged in aviation medicine and related activities. The index lists all FAA aerospace medicine technical reports published from 1961 through 2006: chronologically, alphabetically by author, and alphabetically by subject. A foreword describes the index's sections and explains how to obtain copies of published Office of Aerospace Medicine technical reports. An historical vignette describes some aspects of early toxicological research accomplishments at the Institute.

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Historical Vignette

Fire And Smoke: Improving Aviation Safety Through Combustion Toxicology Research

By William E. Collins, Ph.D., and Katherine Wade, M.L.S.

The historical vignette that follows captures more than two decades of research accomplishments of a biochemistry research team within the Aviation Toxicology Laboratory in the Civil Aeromedical Institute (CAMI). For context purposes, the Toxicology Laboratory (one of several laboratories that originally constituted CAMI's Aeromedical Research Branch) has always comprised a group of research teams identified primarily by their specialty functions. In 2001, CAMI was renamed the Civil Aerospace Medical Institute, and the Toxicology Laboratory became the Bioaeronautical Sciences Research Laboratory.

The vignette represents a self-initiated summarization by Donald Sanders, a research chemist, who developed the material during the 1980s and early 1990s. Its purpose was a means of orienting new laboratory employees on the research activities of Sander's team during the period between 1970-1992. We became aware of the document as a result of publishing a Milestone report of CAMI research in 2005 (DOT/FAA/AM-05/3) when Sanders, who has remained in contact with CAMI personnel since his 1997 retirement, commented that he had prepared some historical material years ago. After reviewing his manuscript, we planned it for inclusion in this issue of the Index, a vehicle previously used to capture historical vignettes, and added some photo documentation.

Donald C. Sanders earned B.S. and M.S. degrees in chemistry from Oklahoma State University and was an instructor there prior to joining CAMI in 1963. His early assignments involved biochemical research on biocidal additives to aircraft fuels (additives that prevented bacterial and fungal growth in the fuel-water interface of the tanks) and issues associated with the exposure of agricultural pilots to the pesticides they used in spraying fields. The latter was an area of particular emphasis in the Toxicology Laboratory during the 1960s. In 1972, Sanders and two long-term associates, John Abbott and Boyd Endecott (both research chemists), began their exploration of combustion toxicology problems in the aviation environment. The team was headed by Charles R. Crane, Ph.D., a biochemist with degrees from the University of Oklahoma (B.S. and M.S.) and Florida State University (Ph.D.). Crane, an assistant professor at Oklahoma State University prior to joining CAMI in 1961, retired in 1988 and was replaced by Arvind K. Chaturvedi in 1990. Chaturvedi obtained his Ph.D. from Lucknow University, India, and had taught at Vanderbilt University and at North Dakota State University.

During the 5-year period from the end of his historical summary to his retirement from federal service, Sanders (along with Endecott, who retired in 2000) remained a part of the new Biochemistry team where he addressed new tasks including drug/altitude effects and aeromedical aspects of melatonin. He also continued his work on combustion toxicology problems with an emphasis on determining coefficients that would allow prediction of time-to-incapacitation for various mixtures of carbon monoxide and hydrocyanic acid — the principal toxic gases produced by fire in aircraft cabins.

Sander's initial research at CAMI included studies of a biocidal boron-containing additive for aircraft fuels (left) and of plasma-cholinesterase levels in agricultural pilots (crop dusters) exposed to organophosphate pesticides (right).

Combustion Toxicology Research in the Biochemistry Research Unit, CAMI, 1970-1992

By Donald C. Sanders

BACKGROUND

In the early 1960s, aeromedical scientists became aware of the possible significance of smoke toxicity to survival in postcrash aircraft fires. It was observed that some victims with no impact-related physical injuries died as a result of the ensuing fire. The inevitable questions arose as to what killed them, how could this be proven, and how could this risk be reduced or even prevented in future crashes. The Civil Aeromedical Institute's (CAMI's) Forensic Toxicology Unit, within the Aviation Toxicology Laboratory in the Aeromedical Research Branch, found that victims from such fire accidents invariably had elevated blood carboxyhemoglobin (COHb) levels, indicating inhalation of carbon monoxide (CO) from the fire. In early 1969, the Biochemistry Research Section (then a "unit" comprised of Charles Crane, Ph.D., and a staff of Donald Sanders, Boyd Endecott and John Abbott) became interested in the observation that such COHb values ranged from 35 to 85 percent saturation levels. The obvious questions were: What is the minimal lethal COHb value, and, if CO was not responsible for the death of victims below such values, why did they die? Since there was a possibility that some of the reported COHb values might be in error, our first investigation was an evaluation of the analytical techniques commonly used in standard forensic toxicology laboratories. We found that for postmortem analysis under anything less than ideal conditions, the use of the established colorimetric procedures could introduce considerable error. A substitute gas chromatographic technique was therefore recommended.

A PROGRAM OF BASIC STUDIES

CAMI's Biochemistry section became directly involved following an impact-survivable accident at Anchorage, Alaska, in 1970. A Capitol International Airways DC-8 had crashed on takeoff (1), and blood specimens from the victims of the ensuing postcrash fire were found to contain cyanide (2). We then undertook a systematic study of the inhalation of both CO and hydrogen cyanide (HCN), using experimental laboratory animals, to establish some basic relationships for these gases. Although it was now recognized that CO was a probable cause of death in smoke inhalation, the emotional impact of discovering highly toxic **cyanide** in the blood of accident victims affected public opinion enough to require actual research into its origin in aircraft fires.

At that time, little was known about the potential of various aircraft interior components for producing toxic combustion gases in a fire. It was surprising that little documented data existed pertaining to the relative human toxicity of the individual combustion gases themselves. The existing analytical methods, particularly for HCN, lacked specificity, sensitivity and/or reproducibility. Questions regarding the concentrations of CO and HCN produced in aircraft fires and their relationship to the postmortem findings of blood cyanide and carboxyhemoglobin remained essentially unanswered.

Our first animal study was a joint project with Wright-Patterson Air Force Base in Ohio to determine 5-min LC_{50} (a dose lethal to 50% of those exposed) values for CO and HCN and to analyze tissue cyanide levels in rats exposed to these specific concentrations of HCN. The resulting analyses convinced us that the then-current methods for measurement of tissue cyanide were completely inadequate. We therefore modified a gas chromatographic detector (converted a flame ionization detector to a nitrogen-phosphorus detector) and developed a method for HCN determination that exceeded the existing colorimetric, fluorometric, and specific electrode standards for specificity and sensitivity. Research in 1970-1972 was devoted to developing methods for determining CO and HCN in chamber atmospheres and in the blood of exposed animals, developing suitable standards for hemoglobin determination, and studying the effects of blood storage conditions on COHb and cyanide content. During 1973, we further refined our sampling and analytical techniques and looked briefly at rhodanese inhibitors to improve storage stability of HCN in blood and tissue samples.

Finally, in early 1974, we began our first in-house rat exposures to HCN, using a 205-L chamber designed by the section personnel and built in the Civil Aeromedical Institute shop. The chamber employed insert cages for LC_{50} determinations and less conventional, motor-driven rotating cages for the determination of incapacitation. Our approach to the measurement of combustion gas effects differed from that of conventional toxicologists in that we realized that

the widely accepted LC_{50} values were of limited application when estimating escape time from a fire environment. We required the definition of the time dependence of the toxic gases on living organisms. We elected to look for the occurrence of psychomotor failure, or physical incapacitation, as our principal endpoint, because that would signal the end of an individual's effective efforts toward unassisted escape from an aircraft. A second deviation from convention was the decision not to count the numbers of rats incapacitated or expired in an arbitrary time period, but to measure the interval between the beginning of exposure and the occurrence of incapacitation or death for each rat (3).

For these initial studies, HCN was generated **in situ** by mechanically injecting a sodium cyanide solution into stirred 10% sulfuric acid inside the chamber. CO exposures were accomplished by injecting commercially available 100% tank CO into the chamber with a 2.8-liter "syringe" of our own construction. By the end of March 1974, we had performed triplicate exposures to CO, to HCN, and to a CO-HCN mixture. These early studies, although crude by today's standards, did serve to justify our choice of a physiological end point; time-to-incapacitation (t_i) occurred at a fraction of the corresponding time-to-death (t_d).

During the following six months, we continuously refined our exposure methodology and analytical techniques, investigated gender-related susceptibility (in rats) to CO and HCN, and performed parallel analyses for HCN by colorimetric and gas chromatographic methods. Two important applications were developed during that period. First, the "dose" for the purpose of defining dose-response relationships in inhalation toxicology, is historically defined as the concentration of the gaseous agent plus an additional parameter, the time over which the exposure takes place. By integrating the area under our concentration-vs-time curves from zero to t_i, we were able to define a "dose," actually a concentration-time product, that was related to a specific t_i. The second application utilized Guyton's relationship of minute-respiratory-volume (MRV) to animal weight in different animal species (4). Assuming that an incapacitating "dose" would be the same for rats of equal weight and that dose, divided by the animal weight, would give us the incapacitating dose per unit of body weight, we developed an equation relating dose, concentration, time, and weight of the animal. Thus, an incapacitating dose, D, could be expressed as $D = [C \bullet t \bullet MRV]/Wt$, where C = concentration in ppm, $t = t_i$, MRV = minute respiratory volume in cm^3/min, and Wt = animal weight in grams (5,6). The equation was equally valid for changing concentrations if the $C \bullet t$ product for the integrated area between zero and t_i were used to replace C and t in the formula. This provided the capability to predict biological responses between species for toxic gases whose mechanism of action was a stoichiometric reaction with critical tissue elements, and hence proportional to total body mass. More pertinent was the exciting possibility of comparing research on nonhuman species to the limited data on human exposures to combustion gases. For CO at least, our calculated physically incapacitating dose for a human, as extrapolated to a 70-kg rat, agreed with the dose predicted by Peterson and Stewart (7) for human acquisition of a 46.5% COHb saturation (8).

A SHIFT TOWARD MATERIALS TESTING

Initially, our research had been directed toward determining basic information about individual combustion gases. The eventual goal was aimed at converting speculative observations into predictive science. Then, in late 1974, the FAA's Office of Aviation Medicine requested that we attempt to assess the relative toxic potential for numerous aircraft interior materials by exposing animals to their pyrolysis products. The request stipulated that the pyrolysis system be similar to one employed at the FAA Technical Center in New Jersey (now the William J. Hughes Technical Center) to allow correlation of our biological findings with the chemical analysis of pyrolysis mixtures to be accomplished by the Technical Center scientists.

This test exposure by Endecott was performed with CAMI's small, flow-through tubular furnace.

In designing our own system (8), we drew heavily on our previous experience with pure gases. Chamber volume was kept at a minimum to reduce the quantity of sample material needed. The isothermal heating regimen was sufficient to ensure thermal degradation of all organic components in the samples (600°C), and the combustion products were rapidly conducted into the exposure chamber. Oxygen concentration in the chamber was maintained above 90% of ambient, and

the temperature was maintained below 35°C. We selected a maximum exposure period of 30 minutes to keep the carbon dioxide concentration below 5% and to minimize the effect of metabolic detoxification on animal response.

Over the course of the year, beginning in mid-1975, we performed triplicate tests on 75 aircraft interior materials and rank-ordered them based on relative t_i and on t_d. We investigated changes in relative rank order when t_i and t_d response times to equal material weights were compared to the orders obtained when rearranged to reflect the **loss** of equal weights during pyrolysis. We also calculated response times corrected for both differences in animal weights and sample weights to define the merits of selecting one system over another for a specific application. We compared different materials within their functional types, i.e., foams, insulations, elastomers, etc. Overall relative standard deviation for the t_i responses for all materials was 13-14%, thus proving the reproducibility of the system for making toxicity measurements of gaseous environments, although the thermal decomposition process did not necessarily represent the actual processes existing in a "real" fire.

Testing the 75 materials proved to be a true learning experience. We had shown (to ourselves, at least) that bioassay could produce very precise endpoints. Deviation from the mean value for 9 rat responses was usually less than 5%, even though individual groups of 3 rats were exposed a month or more apart. It appeared that animals exposed to the same mixture of toxic products on successive occasions reacted the same, and that extreme deviations were related to variations in the combustion process. Materials producing extremely variable results were usually composites, such as layered panels or mixtures of non-uniform composition, that offered sampling difficulties. It was apparent that we had inadequate knowledge about the dynamics of combustion. While we suspected that both the rate of generation and composition of combustion gases would vary with the temperature, oxygen supply, and presence or absence of an ignition source, we had little hard data from the fixed set of conditions imposed on the previous study.

Our next major effort was directed toward developing a new combustion system where sample heating could be programmed, airflow could be controlled over the decomposing sample, and a controllable ignition source could produce flaming or non-flaming combustion as desired. Concurrently, we pursued research to identify the variables of a small-scale test for toxicity. The variables included such diverse factors as effects of carbon dioxide inhalation on breathing rate (and its subsequent effect on t_i when combined with other toxicants), preliminary animal exposures to hydrogen sulfide and sulfur dioxide, and the determination of minimum t_is from high concentrations of CO and HCN to further refine our equation for the describing t_i-vs-concentration curves. We also developed a smoke detection unit for the combustion system that would record smoke density-vs-time during individual material tests.

In 1977, the Biochemistry Section began a study of the toxic potential of 14 state-of-the-art insulating materials for electrical conductors sponsored by the Urban Mass Transportation Administration (9). These materials were selected from a larger group of insulations being evaluated by the Boeing Commercial Airplane Company for properties other than toxicity. Although we determined rat response per unit weight of insulation, we normalized the data to response per unit length of conductor to permit comparison of insulated conductors on the basis of their intended end use. This study utilized our modified 2-inch diameter combustion tube, wrap-around heating units, and a spark igniter. The system allowed us to investigate differences in animal response times to combustion gases produced during three different heating conditions: 1) low-temperature, nonflaming; 2) low-temperature flaming with hot-wire ignition; and 3) high-temperature, flaming at 750°C with or without ignition. Differences in response times noted at different combustion conditions prompted the proposal that materials should be tested at several conditions and ranked on the "worst case performance" found.

OUR INFLUENCE EXPANDS

During this period (1977-78), section personnel participated in a National Bureau of Standards (NBS) ad hoc committee effort to devise and evaluate a small-scale animal

CAMI's large, rotating cage chamber with a "Potts" furnace was used by Crane for this gas exposure test.

test procedure that could be recommended for identifying materials capable of producing "unusually" toxic combustion products. This effort evolved into an inter-laboratory study in which eight different laboratories separately evaluated a control set of standard materials for their combustion toxicity and compared results. Participation in this evaluation required that we modify our 205-L chamber, previously used for pure gas studies, to accommodate a "Potts furnace" combustion unit in an attached chamber, to develop insert chambers for rats that would allow head-only exposure, and to build a "leg-lift" shock avoidance device to measure the specified incapacitation response. The final protocol was adopted in January 1980; our laboratory participation in the cooperative study was concluded in June of that year. The study, although informative, was not conclusive. The published method (10) was used to compare materials on the basis of the toxicity of their combustion products and modification of the method (11) was recommended "for research and preliminary screening purposes."

The ranking of materials by the original method (10) was generally opposed by the plastics industry. It should be remembered that many, if not most, of the researchers who were participating in method development during that period were associated with the wood and plastics industries. Vested interests influenced many of the suggested cut-off levels for determining "unusually toxic" materials; suggestions of "more toxic than the principal product of the company represented" were common. This concern was not entirely unwarranted. A generally accepted test method, perhaps legally enforced, that indicated the superiority of one product over another, could have a devastating effect on manufacturers of the lesser product. Such an outcome would be clearly unfair if the laboratory test method were not (or could not be) validated by corresponding tests in a large-scale fire.

While participating in the NBS cooperative study, we continued to test some state-of-the-art materials that showed promise for use in aircraft interiors and to perform combustion toxicity tests on a variety of materials when requested by outside agencies. These included foam mattress material from a Columbia, Tennessee, jail fire that killed 42 people, Proban-treated wool for the Civil Aviation Attaché to the British Embassy, safety slide material for the American Safety Equipment Company, and rocket propellants for the Thiokol Chemical Corporation. Our research during 1978 was directed toward establishing the thermal tolerance limits of rats and mice subjected to acute exposures at elevated air temperatures. For this limited study, we built a heated and insulated chamber, equipped with a rotating cage assembly, to evaluate the undefined effects of thermal stress on the rats commonly used in combustion toxicology research (12). Dr. Charles Crane also investigated the limited data on human tolerance limits to elevated temperature and proposed rationales for predicting human escape time in rising temperature environments (13) and predicting human tolerance limits to systemic toxic gases (14, 15). Speculative correlations were made between human incapacitation and postmortem COHb/blood cyanide findings in fire-related aircraft accidents (16).

During 1978-1979, Dr. Crane participated in the discussions of the Special Aviation Fire and Explosion Reduction (SAFER) Committee established by the FAA's Flight Standards Service to recommend ways to improve survivability in post-crash environments (17). This committee, and its individual working groups, represented government, industry, and academia. Recommendations for both short- and long-term solutions for post-crash fire hazard reduction and selection of compartment interior materials were extensively discussed.

IRRITANT GAS STUDIES BEGIN

By mid-1980, we began preliminary studies of irritant gas effects. Hydrogen chloride (HCl) gas is a major decomposition product of halogenated polymers such as polyvinyl chloride and polychloroprene used wiring insulation, seats, and fabrics (18). Initial experiments indicated that we would need a high flow rate of HCl gas through the chamber to maintain a fixed concentration due to the extreme solubility of the gas in aqueous (body) fluids. We built a small (12-L) chamber with an enclosed motor-driven rotating cage, adapted a colorimetric method for quantitating gaseous HCl, and determined the t_i and t_d responses by a series of single rat exposures. Individual rat tests were necessary for whole-body exposures because equilibrium concentrations could not be maintained using multiple animals. The HCl (gas) concentrations required to produce incapacitation proved markedly greater than those reported in the scientific literature of that period and suggested that the literature values for humans might have been based on discomfort indices instead of actual incapacitation (18). We were also able to modify another chamber to allow head-only exposures to HCl (gas) in multiples of four rats/test to examine delayed deaths following fixed time/concentration exposures. This chamber also enabled us to remove animals immediately following death for COHb analysis after exposure to CO and to CO-HCl gas mixtures.

Our modest success with the HCl (gas) study encouraged us to consider another irritant gas, acrolein, that had been reported as a combustion product of certain materials used in aircraft interiors. In March through May of 1981, we

developed a gas chromatographic method for acrolein determination in air and confirmed it by a separate colorimetric analysis. Rat exposures, in the following two months, indicated that concentrations required to produce incapacitation were also greater than those suggested by the scientific literature; equations were derived from our empirical data to allow prediction of t_i and t_d for the laboratory rat (19). It should be noted that our approach to the study of the biological responses to each of the combustion gases included a quantitative mathematical correlation between concentration and response time. We considered that if combustion toxicology was to become a predictive science, this kind of correlation would allow chemical analysis of smoke with subsequent computer modeling to gradually replace rat exposures as a measure of toxicity.

In mid-1981, several accidents involving turboprop aircraft occurred that were believed to have resulted from pilot incapacitation from toxic fumes introduced through the cabin pressurization system. It was alleged that a broken carbon seal in the engine would allow lubricating oil to enter the air compressor section, allowing oil-contaminated air to enter the cabin and causing a degradation of pilot performance. We initiated a study of the effects of the thermal decomposition products of selected petroleum-based and synthetic lubricating oils. We also examined exposure to aerosols of one synthetic lubricant and of paraffin oil. We found that none of the products generated smoke components significantly more toxic than the quantity of CO produced, which, in the engine tests, was reported to be insignificant (20). It also marked our only experience with the laboratory generation of aerosols for animal exposure studies.

Beginning in late 1981, we were requested by the Transportation Systems Center (TSC) to evaluate the toxicity of the thermal decomposition products from six electrical wiring insulations selected from a group of candidate materials by Factory Mutual Research of Norwood, Massachusetts. Evaluation was by the methods used in the 1977 study (9), and a composite ranking for these and the 14 materials in the earlier study was prepared at the request of the TSC technical monitor (21). One additional "halogen-free" wiring insulation was also tested using this method.

The wiring insulation study took up most of the section's activity in 1982. Between material testing sessions, we evaluated soot penetration into the respiratory system of the rat when exposed to smoke from burning polyvinyl chloride pipe. We also found that rats with artificial nasal obstructions were incapacitated by HCl in about half the time required for control rats. A preliminary look at species differences was obtained by exposures of gerbils to CO and to the gases from a modacrylic fabric (a known CO and HCN producer).

Another inhalation toxicology related problem was investigated in 1982 at the request of the Office of Aviation Medicine. The use of dry ice as pellets or powdered forms instead of the previously used block form caused concern about the relative rates of sublimation inside cargo aircraft. Dry ice shipments were believed to pose a particular hazard aboard smaller transport aircraft, where the pressurized cargo and personnel compartments are combined. Using the controlled temperature and humidity chambers of the CAMI Protection and Survival Laboratory, we performed a limited study to relate sublimation rates to dry ice from packaging, temperature, and humidity, and related them to the equation in Advisory Circular AC 103-4 for calculating the maximum allowable weight of dry ice cargo (22).

In 1983, we installed a radiant heat assembly in the combustion plenum of a 205-L chamber to allow us to thermally decompose flat materials (such as panels), using a unidirectional heat application; this would allow multilayered materials to decompose in a sequential manner such as they might in a real fire scenario. A recirculation system was developed to allow airflow around the sample, both to supply oxygen to the burning material and to prevent smoke buildup (with subsequent loss of radiant heat flux at the sample position). Using sample sizes scaled down to the 12.6-L chamber size, we compared rat response times and gas concentration/time curves in the two chambers, thus examining the feasibility for further scale-up to something nearer a real-fire situation. Beginning in October of 1983, we performed extensive toxicity tests on two aircraft seat fire-blocking materials designed to delay the involvement of thermally sensitive polyurethane foam seat cushions in an aircraft fire. Each material was decomposed by unidirectional (radiant heat) and omnidirectional (combustion tube) heat in five distinct thermal environments. Sample size was expressed on the basis of surface area per system volume to equate both the end use function of the materials and the difference in volumes of the test systems (23).

Additional material testing took up most of the Biochemistry section's activity in 1984. In March, we performed combustion tests on 4 wiring insulation samples at the request of the New York City Transit Authority. In June, we began toxicity tests on 9 panels that were concurrently being evaluated for flammability and smoke production at the FAA Technical Center using their C-133 aircraft cabin test assembly. These panels were tested using both flaming and nonflaming conditions, 12.6-L vs 265-L chambers, and unidirectional radiant heat vs omnidirectional radiant and conductive heat (combustion tube). The shortest t_is (i.e., worst case condition) occurred at the highest temperature/heat flux condition for both chambers (24). Late in 1984,

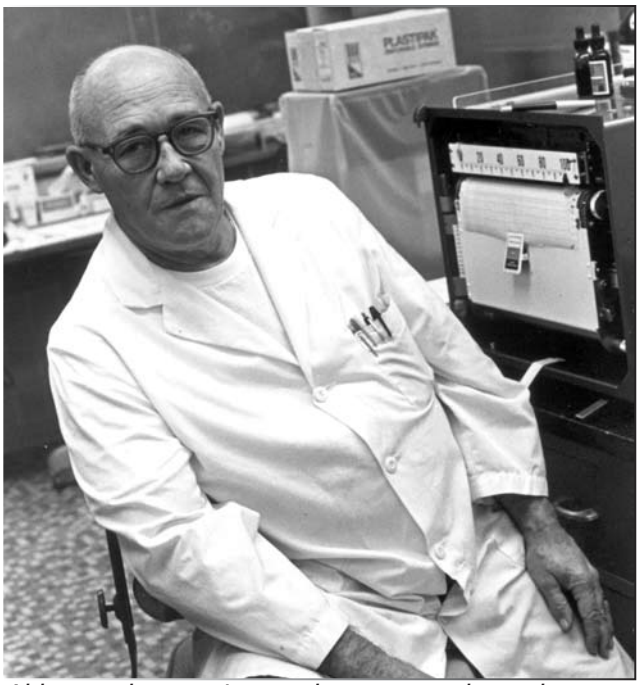
we built an additional radiant heat assembly for use with the combustion tube/small chamber unit to enable us to compare tests in the two systems using similar methods of thermal decomposition.

During this period, the FAA reviewed the possibility that passenger protective breathing devices could be designed for commercial aircraft that would provide some degree of passenger protection from smoke/combustion products and still be compatible with the decompression protective systems in current use. Dr. Crane summarized CAMI's related combustion toxicology research and its application to the problem of survival in inflight aircraft fires in a panel presentation at the 1984 Aerospace Medical Association's annual scientific sessions (25).

A LOOK AT INTERACTIVE EFFECTS

In 1985, we attempted to measure the changes in frequency and amplitude of respiration in the rat with increasing atmospheric carbon dioxide concentrations. With the somewhat crude equipment available, we were able to measure frequency of respiration in an unrestrained rat, but rat movement and cage motion in the rotating cage system prevented integration of the signal to obtain the actual minute respiratory volume. A rat restraining tube, designed for head-only rat exposure, was equipped with an outlet to a pressure transducer, but even the minimal animal movement within the restrainer prevented accurate integration of the respiratory volume with time. The head-only exposure insert restrainer did allow us to study the effects of CO exposures at an elevated chamber temperature (60°C) without raising the animal's core temperature and to measure the corresponding COHb levels at death. We found no statistical difference in the measured parameters between exposures at room temperature and at 60°C.

In late 1985, we acquired a commercial animal exposure chamber containing a rotating "drum" that rotated toward a shock platform; in it, a single rat was required to walk atop the drum to avoid an electrical shock. Early 1986 was spent in fitting the chamber with a flow-through system for introducing gas-air mixtures, in evaluating animal incapacitation in terms of the shock avoidance response, and in adapting a tetracyanonickelate method for the determination of gaseous HCN. These extensive preparations were directed toward a detailed reexamination of the combined effects of CO and HCN on the laboratory rat, a study interrupted some ten years earlier by the agency's material testing requirements. Exposures to CO, HCN, and to mixtures of the two gases occupied the remainder of 1986. Results indicated that the toxic potencies of the two gases were fractionally additive, with no indication of synergism. Dose-response modeling,



Abbott at the team's gas chromatograph used to measure carbon monoxide concentrations in the rat exposure chamber.

based on the concept of "fractional effective doses," was used to devise a mathematical model for estimating t_i produced by defined mixtures of CO and HCN (26). Some material testing continued during this period including a fire-resistant foam produced by Polyvoltac, Canada, and some multi-layer panels manufactured by Schneller, Inc. of Kent, Ohio.

Formal requests for material testing were becoming fewer by 1987, allowing us time to plan experiments that would expand our understanding of the effects of different basic combustion parameters such as gas mixtures, heat, and changes in the pyrolysis process itself. Industry and government were beginning to understand that the ranking of materials on the basis of their potential fire toxicity was a very complex problem and that some of the early approaches to its solution had been overly simplistic. Not enough was known about the combined effects of individual combustion gases to warrant toxicity predictions from the chemical analysis of combustion products, and even with animal models, no laboratory test for fire toxicity of materials had been validated by an equivalent large-scale test model.

One of the unanswered questions involved what the quantitative effect of an irritant gas such as HCl or acrolein might be on the toxicity of the systemic toxicants, CO and HCN. In mid-1987, we began our first rat exposures to CO, acrolein, and CO-acrolein mixtures. We found evidence of an "antagonistic like" effect when acrolein was present in the CO-acrolein mixture at a concentration less toxic than that

of the CO, that is, the t_i was longer than would have been predicted for the CO concentration alone. When the toxic potency of acrolein in the mixture exceeded that of the CO, t_i began to decrease as the acrolein ceased to act simply as a respiration-depressing irritant and began to exert its own toxic effects. Regression equations were developed to predict t_i for the rat when exposed to known concentrations of CO and acrolein, singly and in mixtures (27,28).

The acquisition of a mass flow-controller allowed us to establish a dynamic flow system in an exposure chamber that allowed direct placement of an experimental animal inside the rotating cage after concentration equilibrium had been established. This eliminated the problems of exposing the rat to a changing gas concentration during initial buildup or decay and relating an average concentration to the observed response. A high flow rate through the chamber eliminated any concentration drop at animal insertion. With this modification, we examined the variation in rats' t_i responses to CO at concentrations that produced nominal 5-, 10-, and 25-min t_is; corresponding relative standard deviations were 3, 10, and 19%. This enabled us to refine our CO response equation using more rigidly controlled concentration values.

Some limited material testing continued in 1987. Three panel materials proposed for use in passenger aircraft interiors were tested at the request of the Phillips 66 Company and the Boeing Commercial Airplane Company. Rankings were based on equal surface areas of the sample specimens, again in consideration for their end-use applications (29). We also tested three foam cushion materials at the request of Chestnut Ridge Foam, Inc., one of which had been evaluated as a potential seat blocking material by the FAA Technical Center. Although these tests did not represent any official acceptance or rejection of the foams (no official test criteria existed), copies of the memorandum report of our results, appropriately highlighted and labeled, were distributed by the company as promotional material at a national sales meeting (30). Certain manufacturers and users of the foams used for comparison in the study (which were not manufactured by Chestnut Ridge Foam, Inc.) were not pleased with the use of the report. That venture caused us to consider carefully any future requests for testing of manufacturer-supplied sample materials.

SETBACKS … AND REJUVENATED SUPPORT

In January of 1988, Dr. Charles Crane retired, having been with CAMI since its inception in 1961. His leadership of the Biochemistry Research Section, particularly after the applied research trends directed our efforts toward combustion toxicology, was characterized by a willingness to start with very basic concepts and thus lay the groundwork for the logical progression to applicable knowledge. He was a perfectionist, who believed that any analytical method accepted for use should be checked by at least one other independent method. His approach to combustion toxicology was not that of the conventional toxicologist; he insisted that animal responses be numerically equated with defined gaseous or thermal insults and that the "dose-response" relationships be mathematically modeled to make combustion toxicology a predictive rather than a purely descriptive science. In short, he brought a sense of logic and order to a research field noted for its self-serving and emotional biases.

A significant administrative crisis in the Aeromedical Research Branch led to limited funds for the entire Aviation Toxicology Laboratory in 1988; we were allotted zero equipment money and only $800 for supplies for the year and were now reduced to two researchers, Donald Sanders and Boyd Endecott. John Abbott had previously retired in January 1986. With technical advice from CAMI's Protection and Survival Laboratory personnel, we modified an existing animal exposure chamber to provide a controlled thermal environment and a stable, flow-through CO-air atmosphere. With this equipment, we investigated the effect of moderately elevated, whole-body temperatures on the rat's t_i response to fixed concentrations of CO. Equations were derived from the data to describe the t_i relationships to temperature and CO concentrations, both singly and when simultaneously applied. The fractionally additive incapacitating effects reaffirmed the necessity for temperature control when the rat is used for combustion gas testing (31,32).

In 1989, we studied the relative toxic hazard rankings of identical materials by t_i and by LC_{50}, the principal indices used to measure the toxicity of combustion products. Pure polymeric standards were selected to provide uniformity of sample composition and to allow selection of a broad range of probable gas compositions; combustion conditions were identical for all tests. Relative rankings by the two endpoints were not identical. We found that delayed deaths were possible, even when incapacitation did not occur during the acute exposure and that LC_{50} values give little indication of available escape time in a fire environment. An additional determination of t_is at the experimentally determined LC_{50} values gave a broad range of values for the same set of polymers at this defined condition of equal lethality (33).

Initial plans for 1990 research were to identify the concentrations of CO and HCN that would produce incapacitation in the laboratory rat at 5 and 35 min and to expose a sufficient number of animals to each fixed concentration to determine the variation in the t_i response. This information had been requested for use by a Society of Automotive

Engineers Aviation Working Group that was involved in defining international standards for passenger protective breathing equipment and in which one of the section scientists (Donald Sanders) had previously participated. After Arvind K. Chaturvedi, Ph.D., joined the Biochemistry Research section as supervisor in January 1990, as part of a rejuvenation of support for the entire laboratory, the project was extended to include the measurements of COHb and blood cyanide at t_i. Intermediate experimental results indicated the desirability of determining uptake kinetics for relating blood concentrations with chamber gas concentrations and time. Results indicated that blood concentrations were both time- and concentration-dependent and that no fixed concentration of either blood cyanide or COHb corresponded to the onset of the incapacitation response. The cyanide uptake was essentially linear, and an equation was developed to predict blood cyanide levels in the rat for known exposure times and concentrations. A limited study of rats exposed to CO-HCN mixtures indicated that any effect on individual gas uptake by the second gas in the mixture was minimal (34,35).

Chaturvedi (left) and Sanders combine efforts in setting up the team's small, flow-through combustion assembly.

A SUMMARY OF ACCOMPLISHMENTS

Often in science, what seem to be definitive answers lead to new questions, which lead to new answers, and the cycle goes on. So what did we really accomplish in over 22 years (1970-1992)? Summarizing the preceding chronological record, we developed mathematical relationships from experimental data equating concentrations of the principal combustion gases of importance in civil aviation with t_i using the rat model. For the systemic toxicants, we demonstrated that the dose-response relationships derived from animal studies can be used to calculate dose-response relationships for humans, provided the proper scaling factors are used. Because real fires generate multiple combustion products, we investigated the effects of simultaneous inhalation of two systemic toxicants (CO-HCN) and of a systemic toxicant paired with an irritant gas (CO-acrolein) and developed empirical equations to predict t_i (in the rat) from the relative concentrations of these gases in mixtures. Finally, we quantitatively described the combined effects of elevated temperature and CO concentration on the t_i response in the rat model.

In material testing studies, we investigated different methods of pyrolysis in an attempt to match pyrolysis conditions to a probable condition in a real fire environment. We noted the effects of changes in the burning conditions on the generation rate, composition, and concentration of the resulting combustion gases. Concurrently, we also investigated the specific gases produced, both by chemical analyses and by their biological effects, and compared a variety of physiological endpoints for measuring the relative toxic potencies of polymer combustion products. It became apparent that, whatever testing system was used to rank materials for combustion toxicity, materials must be compared on a quantitative basis related to their end use, i.e., foams by equal volume, panels by equal surface area, wiring insulations by equivalent length of conductor, etc. It was also apparent that all materials needed to be tested in their final formulations, including all coloring materials, fire retardants, and surface coatings, since each of these could (and frequently did) contribute to the toxicity of the resulting combustion gases.

Throughout the studies, we attempted to define each factor in the material combustion/exposure/response relationships in such a way that the information gained could be used to sequentially refine the conditions for succeeding experiments. This stepwise approach also allowed us to mathematically reevaluate data from older studies in the light of our newer findings. The in-house construction of most of the animal exposure chambers, and their subsequent operation, made us painfully aware of their original design shortcomings and allowed us to innovatively improve them to increase the precision of replication in animal exposures.

Perhaps overshadowing these contributions to combustion toxicology are advances that remain to be accomplished. Even today, state-of-the-art combustion toxicology has no generally accepted standard method for ranking materials on the basis of the relative toxicity of their combustion products. There is no "standard" fire condition, nor are there any small-scale laboratory test methods, adequately validated by comparable full-scale fire tests, that will reliably rank competing candidate materials to reflect their overall fire hazard. Regrettably, there has been little, if any, reduction in the use of rats for toxicity testing. Although we developed the products that government requested (and industry frequently resisted), there proved to be few simplistic answers to the abundance of complex problems.

UNFINISHED BUSINESS

Based on our years of experimental research studies, what remains to be done before we can ever hope to meaningfully assess the potential fire hazard of materials by laboratory testing and subsequent mathematical modeling? In the area of material combustion, we must mathematically define the effects of heating rates, types of ignition and amounts of available oxygen on the rate of production, composition, and concentration of combustion products. Any laboratory-scale "test" must be validated by parallel large-scale tests that directly compare defined loads of test materials. In animal testing, it would be desirable to measure the actual uptake of the toxicants, not time-concentration measurements, and to equate these actual doses with specific physiological end points. This would enable us to make judgments on an actual dose-per-unit-weight basis, which would enhance the application of rat data to the human model. We need to examine the actual mechanisms of action for each toxicant on the living organism and its systems and to determine effects of multiple toxicants on the relative uptake of each. Fire-generated aerosols still remain a relatively unexplored problem. How are they generated and what are their biological effects? Accurate mathematical modeling will depend on the quantitative interpretation of each of these cause-effect relationships. Even if the combustion products are of an exposure that does not produce incapacitation or death, what are the long-term health risks that result?

Many of the questions related to the effects of combustion conditions and individual material screening can probably be answered by approaches utilizing a combination of engineering and bioanalytical chemistry techniques. Limited animal testing may still be required to look for the occasional "supertoxic" material that might not be detected in a screening test for expected combustion gases. We also need to remind ourselves that potential fire toxicity is only one problem in the selection of the "safest" materials for aircraft interiors. Material properties such as flammability, tensile strength, durability, cost, and amount of the specific material used, must also be considered if meaningful judgments are to be made. If the material doesn't burn, then smoke toxicity isn't a problem! What we probably should **not** do is require that material selection be regulated solely on the basis of existing, small-scale toxicity tests, which are neither sophisticated nor reliable enough to accurately evaluate acute and long-term toxic hazards for humans.

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Organization

The Index is organized in three sections:

1. Chronological Index: a cumulative list of all research reports from 1961 through 2006.
2. Author Index: all contributing authors, in alphabetical order.
3. Subject Index: subjects, listed in alphabetical order.

Some examples are:

06-8 Williams KW: Human factors implications of unmanned aircraft accidents: Flight control problems.

Above: This is an entry from the ***Chronological Index*** of research reports, shown in cumulative sequence.

Xing J -- --04-17, 05-4, 06-2, 06-6, 06-11, 06-15, 06-22

Above: This is an entry from the ***Author Index,*** which lists all of the research reports prepared by an author or co-author.

Cosmic radiation

...air carrier crew, exposure of, 80-2, 92-2, 00-33, 03-16, 05-14

Above: An example of entries in the ***Subject Index;*** refers to all reports that pertain to a specific topic.

Report Numbers

05-2 Corbett CL: Caring for precious cargo, Part II: Behavioral techniques for emergency aircraft evacuations with infants through the Type III overwing exit. ADA460057

Above: The first numbers (05-2) refer to the year and chronological number of the report. This is an abbreviated portion of the official number given each report and is found in the upper left of the report's cover page. The full report number of "05-2" is DOT/FAA/AM-05/2. The "ADA460057" is appended to the report by the National Technical Information Service. Keep the number system in mind when ordering from NTIS.

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